Gender-related differences in patients presenting with suspected acute coronary syndromes: clinical presentation, biomarkers and diagnosis

Stähli, B E ; Gebhard, C ; Yonekawa, K ; Gebhard, C E ; Altwegg, L A ; von Eckardstein, A ; Hersberger, M ; Novopashenny, I ; Wolters, R ; Wischnewsky, M B ; Lüscher, T F ; Maier, W

Abstract: Objectives: Gender differences in patients presenting with suspected acute coronary syndromes (ACS) have not yet been fully characterized. The aim of this study was to assess gender-related disparities in clinical profiles, biomarkers and diagnoses of patients with suspected ACS. Methods: This single-centre, prospective cohort study included 377 consecutive patients presenting with suspected ACS to the emergency department. Suspected ACS was defined as a request for conventional troponin T (c-cTnT) measurements on clinical grounds. Results: Women were older than men ($p = 0.004$), and had a lower prevalence of known coronary artery and peripheral vascular disease ($p < 0.05$). c-cTnT was positive in 8% of female and in 14% of male patients ($p = 0.16$), TIMI risk score and cardiac biomarkers including c-cTnT, hs-cTnT, myoglobin, creatine kinase, N-terminal pro-brain natriuretic peptide, myeloid-related protein 8/14 and pregnancy-associated plasma protein A were lower in women ($p < 0.05$). Women were less frequently diagnosed with ACS (30 vs. 51%), and were not referred for urgent coronary angiography as often as men ($p < 0.001$). In multivariate analysis, female gender was associated with a lower referral for coronary angiography (HR 0.41, 95% CI 0.23-0.78, $p = 0.006$). Conclusions: In patients with suspected ACS, women presented with different biomarker profiles, and were less often diagnosed with ACS and referred to coronary angiography.

DOI: https://doi.org/10.1159/000435908

Original Research

CARDIOLOGY

Cardiology 2015;132:189–198
DOI: 10.1159/000435908

Received: March 23, 2015
Accepted after revision: June 12, 2015
Published online: August 13, 2015

Gender-Related Differences in Patients Presenting with Suspected Acute Coronary Syndromes: Clinical Presentation, Biomarkers and Diagnosis

B.E. Stähli[a] C. Gebhard[a] K. Yonekawa[a] C.E. Gebhard[a] L.A. Altwegg[a]
A. von Eckardstein[b] M. Hersberger[c] I. Novopashenny[d] R. Wolters[d]
M.B. Wischnewsky[d] T.F. Lüscher[a] W. Maier[a]

[a]Department of Cardiology, University Heart Center and [b]Institute of Clinical Chemistry, University Hospital Zurich, and [c]Institute of Clinical Chemistry and Biochemistry, Childrens Hospital Zurich, Zurich, Switzerland; [d]FB Mathematics and Computer Science, University of Bremen, Bremen, Germany

Key Words
Acute coronary syndromes · Cardiac biomarker · Gender differences

Abstract
Objectives: Gender differences in patients presenting with suspected acute coronary syndromes (ACS) have not yet been fully characterized. The aim of this study was to assess gender-related disparities in clinical profiles, biomarkers and diagnoses of patients with suspected ACS. ***Methods:*** This single-centre, prospective cohort study included 377 consecutive patients presenting with suspected ACS to the emergency department. Suspected ACS was defined as a request for conventional troponin T (c-cTnT) measurements on clinical grounds. ***Results:*** Women were older than men ($p = 0.004$), and had a lower prevalence of known coronary artery and peripheral vascular disease ($p < 0.05$). c-cTnT was positive in 8% of female and in 14% of male patients ($p = 0.16$), TIMI risk score and cardiac biomarkers including c-cTnT, hs-cTnT, myoglobin, creatine kinase, N-terminal pro-brain natriuretic peptide, myeloid-related protein 8/14 and pregnancy-associated plasma protein A were lower in women ($p < 0.05$). Women were less frequently diagnosed with ACS (30 vs. 51%), and were not referred for urgent coronary angiography as often as men ($p < 0.001$). In multivariate analysis, female gender was associated with a lower referral for coronary angiography (HR 0.41, 95% CI 0.23–0.78, $p = 0.006$). ***Conclusions:*** In patients with suspected ACS, women presented with different biomarker profiles, and were less often diagnosed with ACS and referred to coronary angiography.

Introduction

Acute coronary syndromes (ACS) are a major cause of morbidity and mortality in the Western world, both in men and women [1, 2]. Patients with symptoms suggestive of ACS are common in the emergency setting, and assessment of these patients remains challenging due to a wide variety of underlying diseases and an often atypical symptom presentation, particularly in women [3, 4]. Given the diagnostic and prognostic importance of a rapid identification of patients with ACS and of those in need for early coronary revascularization, patient triage at the emergency department is paramount, and is mainly based

B.E.S. and C.G. contributed equally to this work.

Willibald Maier, MD
Department of Cardiology, University Heart Center, University Hospital Zurich
Rämistrasse 100
CH–8091 Zürich (Switzerland)
E-Mail karmaiew@usz.uzh.ch

on clinical parameters, electrocardiography (ECG) changes and biomarker profiles [5–9].

In ACS patients, gender-related differences in presentation and outcomes have previously been reported [10–12], and besides observed disparities in baseline characteristics, associations between atypical symptoms including back pain, nausea and shortness of breath and female gender were identified [3, 4, 13]. Data on gender-related differences, however, are mainly based on the ACS patient population, and studies on unselected patients presenting to the emergency department with any signs and symptoms suggestive of ACS are scare, and have mostly been obtained in primary care or were restricted to chest pain syndromes [14–17]. Furthermore, information on final diagnoses and the proportion of patients undergoing urgent coronary angiography is often lacking. In the heterogeneous patient population presenting with suspected ACS, gender-related disparities in clinical characteristics, biomarker profiles and underlying diagnoses have not yet been fully elucidated. A more thorough characterization of this patient population may expand our understanding of gender-related differences in clinical presentation, and thereby improve patient triage and management in emergency care.

Thus, the aim of this study was to assess gender-related differences in clinical and biomarker profiles, along with the distribution of underlying diagnoses, in patients presenting with symptoms suggestive of ACS.

Methods

Study Design

In the single-centre, prospective, observational MyRiAD (Myeloid Related Protein 8/14 in the Evaluation of Acute Chest Pain in the Emergency Department) study, consecutive patients who presented to the emergency department with any signs and symptoms suggestive of ACS and for whom conventional troponin T (c-cTnT) measurements were requested on clinical grounds, were included from July 2007 to April 2008 [18]. Inclusion criteria were any signs or symptoms suggestive of ACS including chest pain, epigastric pain, dyspnoea, hypotension, lightheadedness, cardiac arrest, palpitations, syncope and nausea as well as a consecutive request by the emergency physician to perform a troponin test to confirm or rule out myocardial ischaemia. Exclusion criteria were symptom onset >24 h, any trauma and any acute or chronic infection. Of 538 patients screened, 377 (70%) were included in the final analyses. The study was conducted according to the principles of the Declaration of Helsinki, and approval to conduct the study was granted by the institutional ethics committee of the University Hospital Zurich. Written informed consent to participate was obtained from all patients.

As previously described [18], patients were assessed at the emergency department, and referral for coronary angiography was left to the discretion of the treating physician, based on the symptoms presented, ischaemic ECG changes and routine biomarker analyses including c-cTnT, myoglobin, creatine kinase (CK), creatine kinase-myocardial band (CK-MB), N-terminal pro-brain natriuretic peptide (NT-proBNP) and D-dimers. Risk assessment was complemented by calculation of the TIMI risk score for unstable angina/non-ST-elevation myocardial infarction or for ST-elevation myocardial infarction, respectively [19, 20]. In patients presenting with chest pain, pain intensity as assessed on a pain scale of 1–10 was recorded. Data on time of symptom onset were collected at the emergency department, together with patient characteristics, and the time point of blood harvesting was registered.

Laboratory Analyses

Laboratory analyses were performed as previously described [18]. In brief, routine markers including c-cTnT, myoglobin, CK, CK-MB and NT-proBNP were analyzed from heparin plasma with a maximal inter-assay variation of 3.7, 2.5, 1.8, 2.8 and 4.4%, and a detection limit of 10.0 ng/l, 21.0 μg/l, 7.0 U/l, 3.0 U/l and 5.0 ng/l, respectively. The cut-off value for positive c-cTnT measurements was 0.10 μg/l. D-dimers were determined from citrate plasma (Roche Modular Analytics System, Roche Diagnostics, Rotkreuz, Switzerland). Study-specific analyses for the MyRiAD study were described previously; they included the levels of myeloid-related protein 8/14 (MRP 8/14), heart-type fatty acid-binding protein (H-FABP), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), myeloperoxidase (MPO), pregnancy-associated plasma protein A (PAPP-A), insulin-like growth factor 1 (IGF-1), fibrinogen and high-sensitivity cardiac troponin (hs-cTnT) [18]. IL-6 and hs-CRP were determined from heparin plasma, and IGF-1 from serum (Immulite 2000 chemiluminescence analyser) using commercial assays from Siemens Healthcare Diagnostics GmbH (Deerfield, Ill., USA) with a maximal inter-assay variation of 2.7, 3.1 and 4.5%, and a detection limit of 1.5 ng/l, 0.3 mg/l and 3.0 μg/l, respectively. PAPP-A was measured immunochemically by time-resolved amplified cryptate emission (TRACE) from serum (Kryptor analyzer, Brahms AG, Hennigsdorf, Germany), with a maximal inter-assay variation of 4.7% and a limit of detection of 0.004 U/l. Fibrinogen was determined on a CA7000 analyser (Siemens Healthcare Diagnostics GmbH) using commercial assays with a maximal inter-assay variation of 4.8%. MRP 8/14 was measured from serum using dedicated assays (Bühlmann Laboratories, Schönenbuch, Switzerland) with a limit of detection of 0.4 μg/ml and a cut-off value of 4.7 μg/ml. H-FABP levels were analyzed from serum using specific assays (Hycult Biotechnology, Uden, The Netherlands) with a detection limit of 0.1 ng/ml and a cut-off value of 5 ng/ml. Samples were tested in double determination, and if the values differed by >10%, the measurements were repeated, unless absorbance was <0.1 or both concentration values were within the normal range. hs-cTnT was measured from serum utilizing the Elecsys assay (Roche Diagnostics, Mannheim, Germany) with a detection limit of 5 pg/ml and a cut-off value of 13 pg/ml, and MPO was measured from heparin plasma with assays from Immundiagnostik (Bensheim, Germany) with a detection limit of 1.6 ng/ml.

Statistical Analysis

Continuous variables are presented as mean ± SD or median and interquartile range (IQR), and categorical variables given as frequencies and percentages. Normal distribution was tested by the Shapiro-Wilk test. Continuous variables were tested for differences with the Mann-Whitney U test and categorical variables by the Pearson χ^2 test or the Fisher exact test as appropriate. A step-

Table 1. Baseline characteristics

Characteristics	All patients (n = 377)	Female patients (n = 102) (27)	Male patients (n = 275) (73)	p value
Age, years	60 (51–71)	65 (54–75)	59 (49–70)	**0.004**
Family history of CAD	105 (28)	29 (28)	76 (28)	0.90
Dyslipidemia	173 (46)	39 (38)	134 (49)	0.08
Diabetes	63 (17)	17 (17)	46 (17)	1.00
Hypertension	214 (57)	61 (60)	153 (56)	0.49
Current smoker	110 (29)	13 (13)	97 (35)	**<0.001**
BMI	26.5 (24.0–29.4)	25.6 (23.0–28.9)	26.8 (24.6–29.7)	**0.007**
Previous MI	78 (21)	13 (13)	65 (24)	**0.02**
Previous CABG	28 (7)	3 (3)	25 (9)	**0.047**
Previous PCI	82 (22)	15 (15)	67 (24)	**0.049**
Peripheral vascular disease	36 (10)	4 (4)	32 (12)	**0.03**
Cerebrovascular disease	31 (8)	12 (12)	19 (7)	0.14
eGFR, ml/min	92 (69–118)	72 (54–94)	96 (77–123)	**<0.001**

Results are given as median (IQR) or n (%). Figures in bold type are significant. BMI = Body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; PCI = percutaneous coronary intervention. p ≤ 0.05 denotes a significant difference between female and male patients.

wise logistic regression analysis by the backward Wald method including all variables with p values <0.20 in univariate analysis was used to determine independent predictors of referral for coronary angiography in multivariate analysis. All tests were 2-tailed, and a p value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM-SPSS version 21 (IBM Corp.) for Windows.

Results

Demographic Characteristics

Out of 377 consecutive patients presenting with suspected ACS to the emergency department, 102 (27%) were women. Women were older than men (p = 0.004), and were significantly overrepresented in the elderly patient group, i.e. >75 years (p = 0.01; fig. 1). Women had a lower body mass index (p = 0.007) and were less frequently current smokers (p < 0.001). Other baseline cardiovascular risk factors including diabetes, dyslipidemia, hypertension and a family history of coronary artery disease did not differ between genders. Known coronary artery and peripheral vascular diseases were less frequently observed in female than in male patients (p < 0.05), while the prevalence of cerebrovascular disease was similar (table 1). Estimated glomerular filtration rate was lower in females than in males (p < 0.001; table 1). Medication at presentation including antiplatelet therapy, antihypertensive

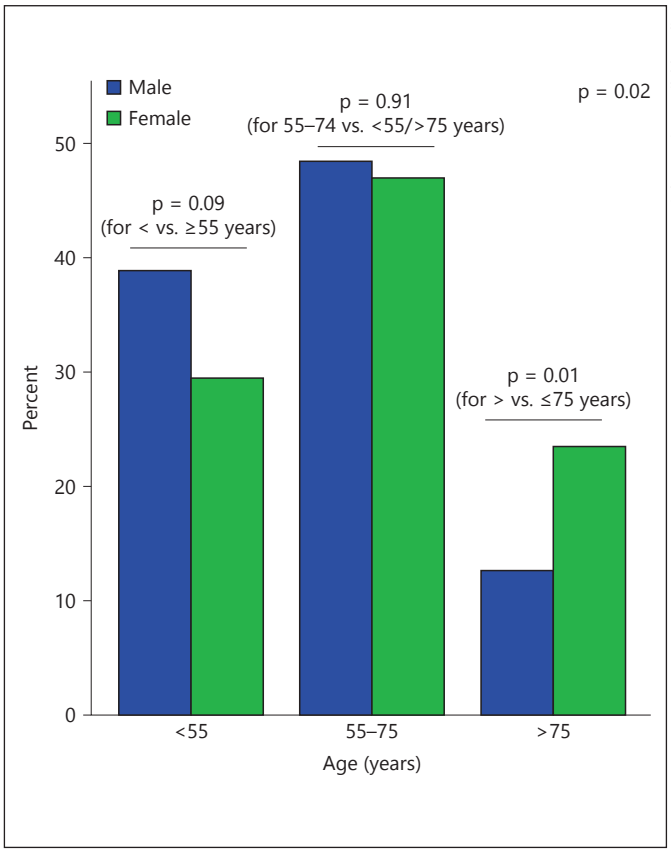


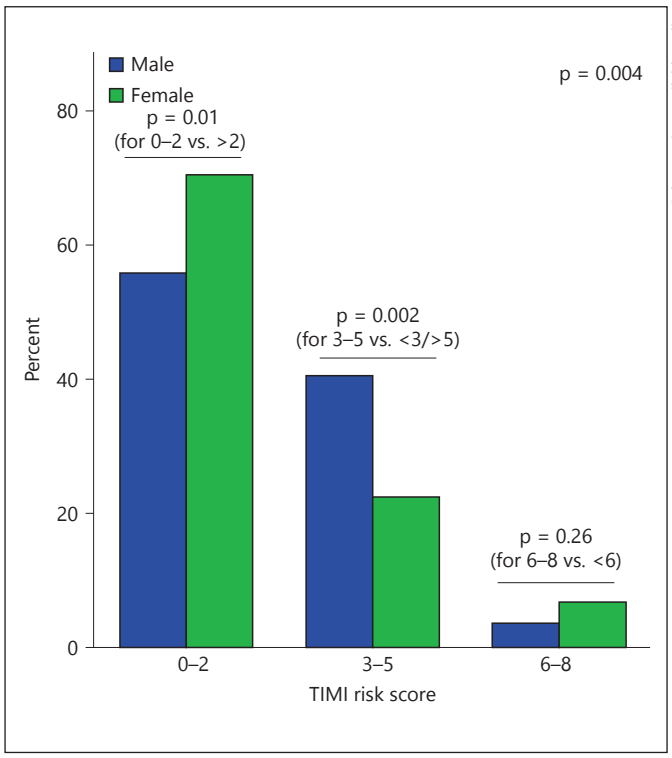
Fig. 1. Age distribution according to gender. p ≤ 0.05 denotes a significant difference between female and male patients.

Cardiology 2015;132:189–198
DOI: 10.1159/000435908

Table 2. Baseline medications

Medication	All patients (n = 377)	Female patients (n = 102) (27)	Male patients (n = 275) (73)	p value
Aspirin	147 (39)	34 (33)	113 (41)	0.19
Clopidogrel	36 (10)	10 (10)	26 (10)	1.0
Dual anti-platelet therapy	27 (7)	8 (8)	19 (7)	0.82
ACE inhibitor	83 (22)	23 (23)	60 (22)	0.89
Beta-blocker	149 (40)	42 (41)	107 (39)	0.72
CCB	52 (14)	20 (20)	32 (12)	0.06
Statins	130 (37)	28 (28)	102 (35)	0.09

Results are given as n (%). ACE = Angiotensin-converting enzyme; CCB = calcium channel blocker. $p \leq 0.05$ denotes a significant difference between female and male patients.



Color version available online

Fig. 2. TIMI risk score according to gender. $p \leq 0.05$ denotes a significant difference between female and male patients.

agents and statins did not differ between genders (table 2).

Compared with men, TIMI risk scores were lower in women (p = 0.004; fig. 2). Of the female patients, 71, 22 and 7% were in the TIMI risk score groups 0–2, 3–5 and 6–8, respectively. Of the male patients, 56, 40 and 4% were in the TIMI risk score groups 0–2, 3–5 and 6–8, respectively.

Symptoms and Biomarkers at Presentation

Mean pre-hospital time delay was 404 ± 375 min for women and 381 ± 317 min for men, respectively (p = 0.59). Most patients presented during hours of daytime (06.00–18.00). Women presented more often during the night hours (18.00–06.00), and men more often during the day (06.00–18.00, p = 0.02; fig. 3). While chest pain was equally reported in both female and male patients (86 vs. 89%; p = 0.59), nausea tended to be more frequent in women (31 vs. 24%, p = 0.08). Vertigo (24 vs. 27%; p = 0.30) and syncope (8 vs. 8%; p = 1.0) were equally reported. In patients with chest pain and documented information on pain intensity (n = 317), pain intensity was equally reported in both women and men (p = 0.97; fig. 4).

c-cTnT at admission was positive in 8% of female and in 14% of male patients (p = 0.16), and hs-cTnT in 32% of female and 50% of male patients, respectively (p = 0.002). Besides CK-MB, all cardiac biomarkers were lower in females than in males (table 3). Out of the 7 inflammatory biomarkers measured, MRP 8/14 and PAPP-A were significantly lower in females than in males, while other markers did not differ between genders (table 3). Comparing hs-cTnT-positive and hs-cTnT-negative patients, besides IGF-1, all of the inflammatory biomarkers including MRP 8/14 and PAPP-A were higher in patients with elevated troponin levels (p < 0.001).

Diagnostic Spectrum

Of the patients presenting to the emergency department with suspected ACS, the initial diagnosis of ACS was made in 31/102 (30%) female and in 141/275 (51%) male patients. Men presented more often with ST elevations (20%; n = 56) than women (13%; n = 13; p = 0.05). Fifty percent (n = 136) of male and 28% (n = 29) of female

Table 3. Cardiac and inflammatory biomarkers

Biomarkers	All patients (n = 377)	Female patients (n = 102) (27)	Male patients (n = 275) (73)	p value
Cardiac				
CK, U/l	115 (76–183)	82 (57–132)	126 (88–208)	**<0.001**
CK-MB, U/l	18 (13–27)	16 (12–25)	18 (13–28)	0.28
Myoglobin, µg/l	46 (32–77)	35 (27–60)	48 (34–91)	**<0.001**
c-cTnT, µg/l	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	**0.049**
hs-cTnT, pg/ml	11.6 (4.7–33.0)	7.0 (3.2–19.3)	14.4 (5.6–38.9)	**<0.001**
NT-proBNP, ng/l	134 (48–674)	174 (89–734)	114 (37–506)	**0.004**
Inflammatory				
MRP 8/14, µg/ml	2.9 (2.0–4.5)	2.4 (1.7–3.4)	3.2 (2.1–4.8)	**<0.001**
PAPP-A, U/l	9.0 (7.0–13.0)	8.5 (7.0–11.2)	9.0 (8.0–13.0)	**0.003**
H-FABP, ng/ml	2.4 (1.4–6.1)	2.1 (1.2–4.7)	2.4 (1.4–6.8)	0.09
hs-CRP, mg/l	2.4 (0.9–5.9)	2.5 (1.1–5.6)	2.4 (0.9–5.9)	0.90
IL-6, ng/l	3.4 (1.9–7.5)	3.3 (1.9–7.3)	3.7 (1.9–7.6)	0.56
MPO, ng/ml	41 (26–68)	38 (25–66)	42 (27–69)	0.49
IGF-1, µg/l	126 (98–157)	123 (100–123)	128 (98–157)	0.79

Results are given as median (IQR). CK = Creatine kinase; CK-MB = creatine kinase-myocardial band; c-cTnT = conventional cardiac troponin T; hs-cTnT = high-sensitivity cardiac troponin T; NT-proBNP = N-terminal pro-brain natriuretic peptide; MRP 8/14 = myeloid-related protein 8/14; PAPP-A = pregnancy-associated protein A; H-FABP = heart-type fatty acid-binding protein; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; MPO = myeloperoxidase; IGF-1 = insulin-like growth factor 1. Figures in bold type are significant. p ≤ 0.05 denotes a significant difference between female and male patients.

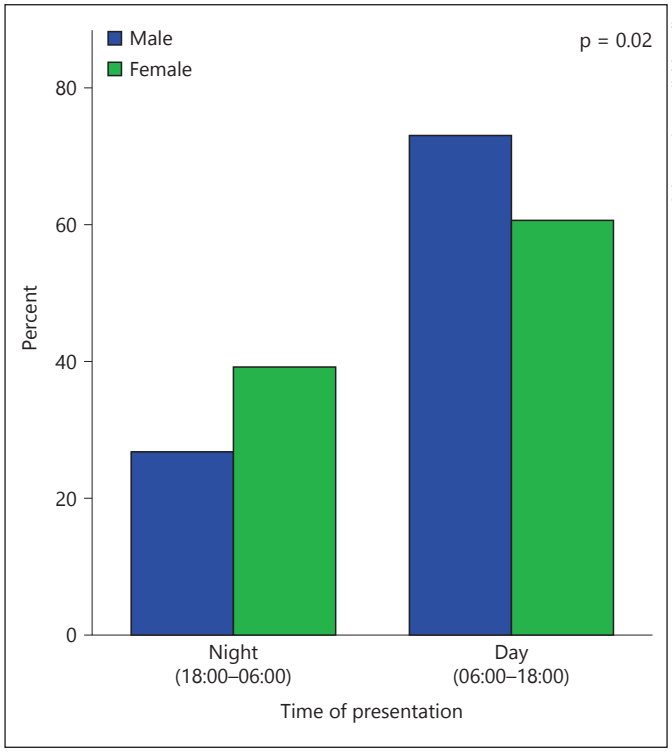


Fig. 3. Circadian presentation of female and male patients with suspected acute coronary syndromes. p ≤ 0.05 denotes a significant difference between female and male patients.

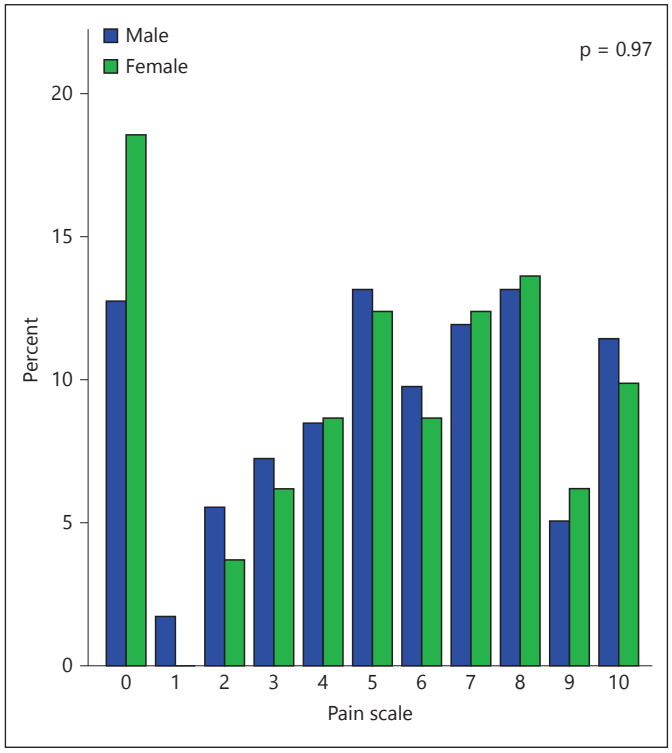


Fig. 4. Chest pain intensity according to gender. p ≤ 0.05 denotes a significant difference between female and male patients.

Cardiology 2015;132:189–198
DOI: 10.1159/000435908

Table 4. Diagnosis and management of coronary artery disease

Patient management and diagnosis	All patients (n = 377)	Female patients (n = 102) (27)	Male patients (n = 275) (73)	p value
Patients with coronary angiography	165 (44)	29 (28)	136 (50)	<0.001
Coronary revascularization	127 (34)	18 (19)	109 (40)	<0.001
PCI	123 (33)	18 (18)	105 (38)	
CABG	4 (1)	0 (0)	4 (1)	
Medical management of ACS	3 (1)	0 (0)	3 (1)	
Patients without coronary angiography				
Medical management of ACS	7 (2)	2 (2)	5 (2)	
Final diagnosis of ACS	137	20 (20)	117 (43)	<0.001

Results are given as n (%). CABG = Coronary artery bypass grafting; CAD = coronary artery disease; PCI = percutaneous coronary intervention. $p \leq 0.05$ denotes a significant difference between female and male patients.

patients underwent coronary angiography ($p < 0.001$). Referral for coronary angiography was similar in younger (≤65 years) and elderly (>65 years) patients (43 vs. 45%; $p = 0.67$). Patients with known coronary artery disease ($p < 0.001$), ≥3 cardiovascular risk factors ($p < 0.001$) and ≥2 anginal episodes within the last 24 h ($p < 0.001$) were more frequently referred for invasive assessment, along with troponin-positive patients ($p < 0.001$) and patients with ST-segment changes ($p < 0.001$).

In patients referred for coronary angiography, subsequent coronary revascularization was performed in 18 (19%) women and 109 (40%) men ($p < 0.001$). Percutaneous coronary revascularization was performed in 18 (18%) female and in 105 (38%) male patients, and coronary artery bypass grafting within 14 days in 4 (1%) male patients, respectively (table 4). Three patients diagnosed with coronary artery disease were treated medically without any coronary revascularization. Two patients (1 female and 1 male) were diagnosed as having Takotsubo cardiomyopathy. One male patient with ST-elevations died before coronary angiography could be performed. Hence, 137 (36%) patients were finally diagnosed with ACS, i.e. 20 (20%) female and 117 (43%) male patients ($p < 0.001$; table 4).

The initial diagnosis of arrhythmia was more frequently made for females (n = 14, 14%) than for males (n = 18, 7%, $p = 0.04$). Hypertension tended to be more frequent in women (n = 9, 9%) than in men (n = 11, 4%), albeit without reaching statistical significance ($p = 0.07$). Musculoskeletal chest pain [15 females (15%) vs. 35 males (13%); $p = 0.61$] and 'unspecific symptoms' were diagnosed equally in both genders [14 females (14%) vs. 33 males (12%); $p = 0.73$]. Final diagnoses varied significantly among gender ($p = 0.03$; fig. 5). Coronary artery disease was less often diagnosed in women than in men ($p < 0.001$), while hypertension ($p = 0.12$), arrhythmias ($p = 0.18$), 'unspecific symptoms' ($p = 0.16$), musculoskeletal chest pain ($p = 0.51$), syncope ($p = 0.26$) and gastrointestinal diseases ($p = 0.54$) were equally reported.

In the low-risk group (TIMI risk score ≤2), 17% of female and 28% of male patients were referred for coronary angiography ($p = 0.07$), in the intermediate risk group (TIMI risk scores between 3 and 5), percentages reached 48 and 78% ($p = 0.02$), and in the high-risk group (TIMI risk score ≥6), 86 and 100% ($p = 0.39$), respectively. In multivariate regression analysis, the association between female gender and referral for coronary angiography remained significant when controlling for age, chest pain, positive c-cTnT, TIMI risk score, hypertension and dyslipidemia (table 5). While in male patients, chest pain ($p = 0.005$), positive c-cTnT ($p = 0.04$) and TIMI risk score ($p < 0.001$) were independent predictors of referral for coronary angiography, in female patients, this applied only to the TIMI risk score ($p = 0.02$). Including patients with positive hs-cTnT only, female gender remained an independent predictor of lower referral for coronary angiography (HR 0.33, 95% CI 0.12–0.94, $p = 0.04$) in multivariate analysis.

Discussion

This study demonstrates that in patients with suspected ACS, women were less likely to have cardiovascular comorbidities, presented with different biomarker profiles and had a different diagnostic spectrum. Women

Table 5. Univariate and multivariate logistic regression analysis for coronary angiography

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.01	1.00–1.03	0.12	0.97	0.95–1.00	**0.002**
Dyslipidemia	1.78	1.18–2.69	**0.006**	0.90	0.51–1.59	0.72
Hypertension	2.28	1.49–3.48	**<0.001**	1.29	0.73–2.30	0.38
Diabetes	1.30	0.76–2.24	0.34			
Female gender	0.41	0.25–0.66	**<0.001**	0.49	0.26–0.93	**0.03**
Smoking	0.96	0.57–1.62	0.89			
TIMI risk score	2.46	2.02–3.00	**<0.001**	2.53	1.99–3.21	**<0.001**
Elevated c-cTnT	17.76	6.22–50.72	**<0.001**	8.46	2.56–27.97	**<0.001**
Chest pain	7.44	2.87–19.33	**<0.001**	4.23	1.46–5.16	**0.002**

Figures in bold type are significant.

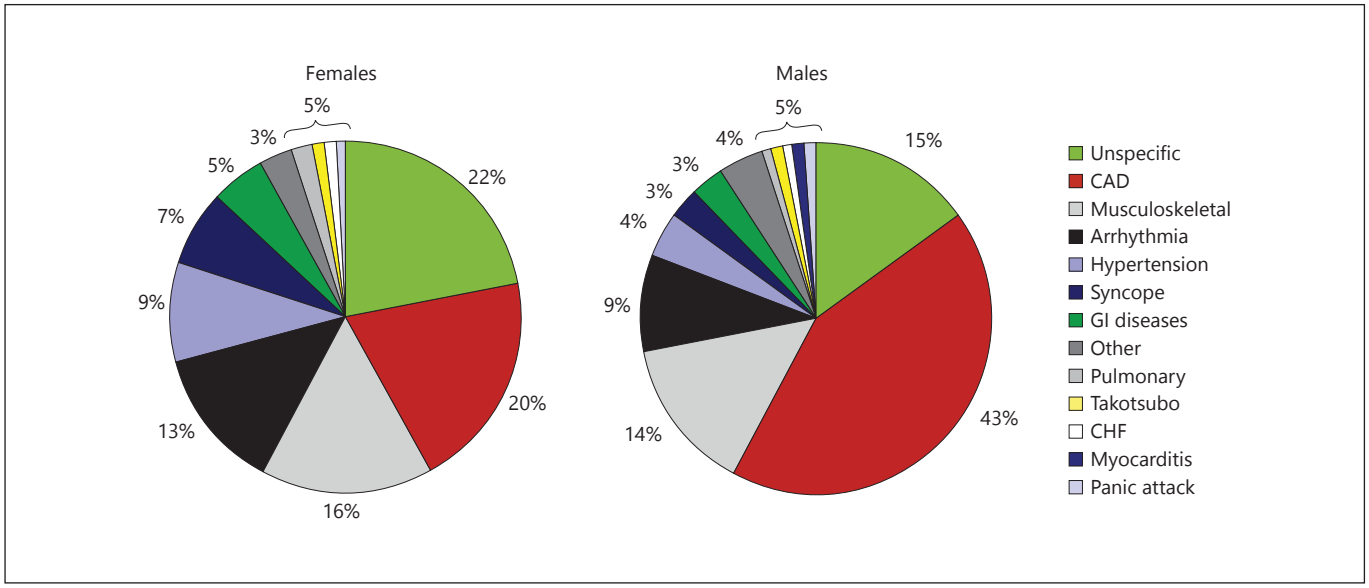


Fig. 5. Final diagnoses for female and male patients. CAD = Coronary artery disease; CHF = congestive heart failure; GI = gastrointestinal.

were less often referred for coronary angiography, and were mostly diagnosed with 'unspecific symptoms'. While symptom duration was similar between genders, a circadian difference with regard to the time of presentation to the emergency department was observed, with women presenting predominantly during the night hours.

Cardiac biomarkers including c-cTnT, hs-cTnT, myoglobin, CK and NT-proBNP were lower in women than in men, consistent with the lower rate of ACS in women. The finding that all inflammatory biomarkers besides IGF-1 were increased in patients with positive hs-cTnT levels, but only MRP 8/14 and PAPP-A were lower in women in agreement with a lower ACS rate, points towards gender-related differences in the regulation of inflammatory biomarkers.

Similar proportions of female patients have previously been reported in emergency department studies enrolling chest pain patients [14, 21], while in primary care, the proportion of women tended to be higher [15, 16], main-

ly due to the lower-risk patient population encountered in outpatient care. In line with data on chest pain patients [21], most patients presented during the day. The higher percentage of women presenting during night hours differs from another emergency department-based study that reported a similar circadian pattern among chest pain patients irrespective of gender [21] ; this may, at least in part, have been attributed to variable patient characteristics, inclusion criteria and study designs.

Referral for coronary angiography increased with increasing TIMI risk scores, and hence, clinical decision-making seems to be influenced by a comprehensive analysis of different cardiovascular risk factors, along with cardiac biomarkers and ECG changes. Age per se does not seem to explain differences in referral rate for coronary angiography in different TIMI risk score groups, as referral for invasive assessment did not differ among younger and elderly patients, along with an HR for age of 0.97 in multivariate regression analysis.

Women were less often referred for coronary angiography and less often diagnosed with ACS than men. This observation may indeed be consistent with lower-risk baseline characteristics, also reflected by the lower TIMI risk score and cardiac biomarker levels observed in women. However, female gender remained independently associated with a lower referral for coronary angiography after adjustment for different cardiovascular risk profiles in multivariate analysis. This finding suggests some gender bias, in particular, as presenting complaints and pain intensities were equally reported in female and male patients, and gender differences with regard to false-negative diagnoses can rarely be assessed in observational studies. In addition, while no gender differences with regard to referral for coronary angiography were observed in the high-risk group, less women were referred for coronary angiography in the intermediate risk group, and a similar trend was observed in the low-risk group; this finding suggests that gender-related disparities in clinical decision-making may vary between different risk groups. Consistent with this interpretation, it has previously been suggested that differences in presentation and clinical course alone cannot explain gender differences observed in the frequency of referrals for coronary angiography in patients with suspected ACS [17]. However, the study design precludes the conclusion that more women should be referred for coronary angiography to diagnose coronary artery disease and to improve outcomes in patients presenting with suspected ACS, particularly as concerns were raised in patients with non-ST-elevation myocardial infarction in terms of increased mortality rates and bleeding complications in women when routine invasive strategies were applied [22]. Large-scale clinical studies are needed to assess the role of invasive and non-invasive diagnostic modalities, including exercise ECG, myocardial perfusion single-photon emission computed tomography and coronary computed tomography as well as their impact on outcomes.

In this study, women were discharged most frequently with 'unspecific symptoms' followed by coronary artery disease and musculoskeletal chest pain. Data on the diagnostic spectrum in these patients are scarce. In primary care, besides coronary artery disease, chest wall syndromes and psychogenic disorders represented the most frequently observed diagnoses [16].

Baseline characteristics differed significantly between genders, with older age, and a lower prevalence of coronary and peripheral artery disease, along with a lower rate of current smokers, in women. While most studies including patients with confirmed or suspected ACS report comparable gender-related differences with regard to known coronary artery disease, age and smoking history [11, 14], conflicting results have been observed regarding other baseline cardiovascular risk factors [11, 14, 15]. Differences between studies may mainly be due to different inclusion criteria, in particular, whether patients with confirmed or suspected ACS were included, and also due to a lower-risk patient population in primary care. Despite an increased prevalence of coronary artery and peripheral vascular disease in men, no significant differences were found with regard to the use of antiplatelet therapy at baseline. Cerebrovascular disease with a prevalence of 12% in women and 7% in men might, at least in part, have contributed to this observation, but further studies are needed to elucidate these findings. The equal percentage of patients on anti-hypertensive agents and statins may be explained by the comparable prevalence of hypertension and dyslipidemia in both women and men.

In this study, symptom duration was calculated as the time period from reported symptom onset to the beginning of treatment in the emergency department, reflected by the point in time of blood harvesting, and was found to be similar in women and men. Consistent findings were reported in primary care, where pre-hospital time delay from call for help until general practitioner consultation did not differ between genders, while doctor-related delay was longer for women [15]. As data on the time point of the call for help were not available, symptom duration could not be further subdivided. In line with other studies on patients with suspected ACS [15], patients with symptoms lasting >24 h were excluded to allow for an as-

sessment of patients presenting with acute complaints. Hence, these findings cannot be generalized to patients with a longer duration of symptoms.

Most research in this field is based on chief complaints, mainly chest pain, but as women are less likely to present with typical symptoms [23], our study included patients with suspected ACS irrespective of the leading complaint, aiming at an inclusion of a wider, less specific patient population. Interestingly, in patients reporting chest pain, pain intensity did not differ between genders, despite the wide variety of underlying diseases. In studies on acute myocardial infarction, however, higher pain intensity scores have been reported by men [24], while in studies enrolling patients with angina, acute myocardial infarction or chest pain, higher pain intensity is reported mostly by women [4, 25, 26]. Hence, gender disparities in pain perception seem to vary according to the underlying disease.

A limitation of this study is its single center design. As no information was available on the use of non-invasive assessment of coronary artery disease, a comparison between invasive and non-invasive modalities was precluded. Further, we cannot exclude completely that there might be some gender bias with regard to the request of troponin measurements. However, as consecutive patients with suspected ACS were included, the study cohort represents a heterogeneous population of patients that was not limited to chest pain syndromes. The high proportion of patients referred for coronary angiography allowed for confirming or excluding the diagnosis of coronary artery disease by the diagnostic gold standard and not solely based on clinical judgment.

In conclusion, women represented a quarter of patients with suspected ACS, were mostly diagnosed with 'unspecific symptoms', and were less often diagnosed with ACS and referred for urgent coronary angiography. As the association between female gender and lower referral for coronary angiography remained significant after adjustment for cardiovascular risk factors, some gender bias cannot completely be excluded. In clinical practice, physicians need to take into account gender disparities, aiming at an improved selection of diagnostic and therapeutic strategies for both women and men. In addition, further studies are needed to elucidate gender differences with regard to the pathophysiological mechanisms, risk stratification and treatment responses in patients with suspected ACS.

Acknowledgement

B.E.S. was partially supported by grants from the Swiss National Research Foundation (Special Programme University Medicine: No. 33CM30-1241112/1 and No. 3100-068118.02/1). K.Y. was supported by the Zürich Heart House – Foundation for Cardiovascular Research. T.F.L. received research grants and consultant fees from Amgen, AstraZeneca, Biosensor International, Biotronik, Eli Lilly, Medtronic and St. Jude Medical. Biomarker analyses were partially been supported by Roche Diagnostics GmbH.

References

1 Go AS, Mozaffarian D, Roger VL, et al: Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. Circulation 2014;129:e28–e292.

2 Nichols M, Townsend N, Scarborough P, Rayner M: Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 2014;35:2929.

3 Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA, Eagle KA, Global Registry of Acute Coronary Events Investigators: Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart 2009;95:20–26.

4 Thuresson M, Jarlov MB, Lindahl B, Svensson L, Zedigh C, Herlitz J: Symptoms and type of symptom onset in acute coronary syndrome in relation to ST elevation, sex, age, and a history of diabetes. Am Heart J 2005;150:234–242.

5 James SK, Lindback J, Tilly J, Siegbahn A, Venge P, Armstrong P, Califf R, Simoons ML, Wallentin L, Lindahl B: Troponin-T and N-terminal pro-B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy. J Am Coll Cardiol 2006;48:1146–1154.

6 Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, O'Hanesian MA, Wagner GS, Kleiman NS, Harrell FE Jr, Califf RM, Topol EJ: Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. N Engl J Med 1996;335:1333–1341.

7 Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, Wu AH, Christenson RH: National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Circulation 2007;115:e356–e375.

8 Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342–1349.

9 Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, Goldmann B, Katus HA: The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992;327:146–150.

10 Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, Aylward P, Topol EJ, Califf RM: Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med 1999;341:226–232.

11 Rosengren A, Wallentin L, K Gitt A, Behar S, Battler A, Hasdai D: Sex, age, and clinical presentation of acute coronary syndromes. Eur Heart J 2004;25:663–670.
12 Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G, Zheng ZJ, NRMI Investigators: Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA 2012;307:813–822.
13 Goldberg RJ, O'Donnell C, Yarzebski J, Bigelow C, Savageau J, Gore JM: Sex differences in symptom presentation associated with acute myocardial infarction: a population-based perspective. Am Heart J 1998;136:189–195.
14 Hess EP, Perry JJ, Calder LA, Thiruganasambandamoorthy V, Roger VL, Wells GA, Stiell IG: Sex differences in clinical presentation, management and outcome in emergency department patients with chest pain. CJEM 2010;12:405–413.
15 Bruins Slot MH, Rutten FH, van der Heijden GJ, Doevendans PA, Mast EG, Bredero AC, Glatz JF, Hoes AW: Gender differences in pre-hospital time delay and symptom presentation in patients suspected of acute coronary syndrome in primary care. Fam Pract 2012; 29:332–337.
16 Bosner S, Haasenritter J, Hani MA, Keller H, Sonnichsen AC, Karatolios K, Schaefer JR, Baum E, Donner-Banzhoff N: Gender differences in presentation and diagnosis of chest pain in primary care. BMC Fam Pract 2009; 10:79.
17 Chang AM, Mumma B, Sease KL, Robey JL, Shofer FS, Hollander JE: Gender bias in cardiovascular testing persists after adjustment for presenting characteristics and cardiac risk. Acad Emerg Med 2007;14:599–605.
18 Stahli BE, Yonekawa K, Altwegg LA, Wyss C, Hof D, Fischbacher P, Brauchlin A, Schulthess G, Krayenbuhl PA, von Eckardstein A, Hersberger M, Neidhart M, Gay S, Novopashenny I, Wolters R, Frank M, Wischnewsky MB, Luscher TF, Maier W: Clinical criteria replenish high-sensitive troponin and inflammatory markers in the stratification of patients with suspected acute coronary syndrome. PLoS One 2014;9:e98626.
19 Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E: The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000; 284:835–842.
20 Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E: TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation. An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102: 2031–2037.
21 Ekelund U, Akbarzadeh M, Khoshnood A, Bjork J, Ohlsson M: Likelihood of acute coronary syndrome in emergency department chest pain patients varies with time of presentation. BMC Res Notes 2012;5:420.
22 Swahn E, Alfredsson J, Afzal R, Budaj A, Chrolavicius S, Fox K, Jolly S, Mehta SR, de Winter R, Yusuf S: Early invasive compared with a selective invasive strategy in women with non-ST-elevation acute coronary syndromes: a substudy of the OASIS 5 trial and a meta-analysis of previous randomized trials. Eur Heart J 2012;33:51–60.
23 Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, Long T: Symptom presentation of women with acute coronary syndromes: myth vs reality. Arch Intern Med 2007;167:2405–2413.
24 Khan JJ, Albarran JW, Lopez V, Chair SY: Gender differences on chest pain perception associated with acute myocardial infarction in Chinese patients: a questionnaire survey. J Clin Nurs 2010;19:2720–2729.
25 Ghezeljeh TN, Momtahen M, Tessma MK, Nikravesh MY, Ekman I, Emami A: Gender specific variations in the description, intensity and location of angina pectoris: a cross-sectional study. Int J Nurs Studies 2010;47:965–974.
26 D'Antono B, Dupuis G, Fleet R, Marchand A, Burelle D: Sex differences in chest pain and prediction of exercise-induced ischemia. Can J Cardiol 2003;19:515–522.